REMARKS

Entry of the Amendment and reconsideration of the claims is respectfully requested.

Claims 47 and 50 have been amended to correct obvious typographical errors. Claim 47 has been amended to clarify the subject matter of this claim. The support for the amendment can be found throughout the specification including at page 24, line 14 to page 26, line 6. Applicants submit that this amendment does not raise any issues of new matter.

Rejections Withdrawn

Applicants acknowledge the withdrawal of the rejection of claims 1, 8, 9, 11, 19, 20, 33, 30-44 under 35 U.S.C. § 103 as unpatentable over Vaughan et al. in view of Reddy et al. and further in view of U.S. Pat. Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.38, and 41-44 under 35 U.S.C. § 103 as unpatentable over Mallender et al. as evidenced by Gulliver, et al. in view of U.S. Pat. Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.

Applicants acknowledge the withdrawal of the rejection of claims 1, 8, 9, 11, 19, 20, and 30-44 under 35 U.S.C. § 103 as unpatentable over Vaughan et al. in view of Bruynck et al. or Vuillez et al., and further in view of U.S. Pat. Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.

Applicants acknowledge the withdrawal of the rejection of claims 1, 8, 9, 11, 19, 20, and 30-44 under 35 U.S.C. § 103 as unpatentable over Vaughan et al. in view of Reddy et al. and further in view of U.S. Pat. Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.

35 U.S.C. § 112

Claims 33-38, 41-47, and 49-51 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. The Examiner contends that the phrases "at least 98%" and "at least about 98%" are new matter. Applicants respectfully traverse this rejection.

The standard for determining whether an application complies with the written description requirements of § 112, first paragraph, is whether one of ordinary skill in the art recognizes from reading the disclosure that the inventors were in possession of the claimed subject matter as of the filing date. Additionally, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by

the Examiner to rebut the presumption." **MPEP 2163.04.** Applicants remind the Examiner that *ipsis verbimus* support is not necessary to satisfy the written description requirement.

Claims 33-38, 41-45, are directed to methods and host cells for preparing a bispecific antibody wherein the first and second variable light chain domain have at least 98% sequence identity. Claims 47 and 49-51 are directed to methods of preparing a bispecific antibody wherein the light chains have at least 98% sequence identity to each variable light chain domain of a first and second antibody. Claim 46 is directed to a method for preparing a bispecific antibody wherein the antibody variable light chain has at least about 98% sequence identity to an original antibody variable light chain of a first and second polypeptide.

Applicants submit that the disclosure clearly provides adequate written description for the claims. At page 22, lines 22-27, Applicants indicate that light chains have "at least 95% and most preferably 100% identity". Applicants submit that one of skill in the art reading the specification would understand "at least 95%" to also include "at least 98%" sequence identity. Applicants also direct the Examiner's attention to page 97, lines 22-26 of the specification, which explicitly discloses light chains of the invention having both 98% and 99% sequence identity. Thus, Applicants submit they clearly have written description for the term "at least 98%", and respectfully request withdrawal of the rejection on this basis.

With respect to claim 46, the claim no longer recites the term "about". Although Applicants do not acquiesce to the rejection, but in order to expedite prosecution, Applicants have amended claim 46. Thus, Applicants submit that they have addressed the Examiner's rejection and respectfully request withdrawal of the rejection on this basis.

The Examiner also contends that the specification does not describe "an original antibody variable light chain of the first and second polypeptide" as recited in claim 45. Applicants respectfully disagree. As discussed previously, there is no *in haec verba* requirement for providing support for the claims in the specification. **MPEP 2163 I.B.** Rather, claim limitations can be supported not only by language in the specification that is identical to the claim language, but also by implicit or inherent disclosure. Id.

Applicants submit that, in view of these guidelines, the specification clearly provides written support for a method for preparing a bispecific antibody, wherein the antibody variable light chain is identical to "an original antibody variable light chain of the first and second

polypeptide." The Examiner has pointed to page 13, lines 17-21. Applicants further direct the Examiner to page 13, lines 12-21. Applicants submit one of skill in the art reading the specification would readily understand that the reference to an "original light chain of each polypeptide" of line 19 refers to the variable light chain of the first polypeptide and the variable light chain of the second polypeptide. Thus, Applicants submit the specification does describe the claim language of claim 45 and Applicants respectfully request withdrawal of the rejection on this basis.

35 U.S.C. § 102

Claim 47 was rejected under 35 U.S.C. § 102(b) as anticipated by Mallender et al. as evidenced by Gulliver et al. Applicants respectfully traverse this rejection.

Claim 47 is directed to a method of preparing a bispecific antibody comprising culturing a host cell comprising a first nucleic acid encoding a first polypeptide comprising a heavy chain variable domain and a first multimerization domain, and a second nucleic acid encoding a second polypeptide comprising a second heavy chain variable domain and a second multimerization domain, and a third nucleic acid encoding the selected variable light chain domain, wherein the first binding site and the second binding site have the same light chain and wherein the first and second multimerization domains interact to form a bispecific antibody.

Mallender et al. disclose the preparation of a bispecific antibody constructed in a single polypeptide chain where each of the variable heavy and light variable domains that form the different antigen binding sites are connected to one another in a single polypeptide chain. The method of Mallender is very different than that claimed by Applicants. Because the bispecific antibody formed in Mallender is a single polypeptide chain where each antigen-binding site is connected via a peptide, Mallender does not contemplate a first and second polypeptide each having multimerization domains that interact with one another. Such domains are not needed in the bispecific antibody of Mallender, and are neither disclosed nor suggested by Mallender.

The Examiner contends that Mallender et al. disclose a bispecific antibody wherein the antibody comprises multimerization domains, because the definition of "multimerization domains" in the instant specification does not exclude domains interacting via a covalent bond, such as a peptide bond. The Examiner further contends that both the first and second nucleic

acid sequences encoding the portions of the bispecific antibody encode a multimerization domain "which interacts to form a bispecific antibody". Applicants request that the Examiner clearly identify the alleged multimerization domains in the first and second nucleic acid as disclosed by Mallender. Applicants submit, that in the least, the Mallender et al. reference does not disclose such multimerization domains in each nucleic acid.

In addition, Applicants' claim 47 is directed to a bispecific antibody that has a selected variable light chain domain that forms a first binding site with the first variable heavy chain domain and a second binding site with the second variable domain. The light chains of Mallender et al. are not the same light chain, but as described by Gulliver and the Examiner differ from one another.

The Examiner further states that Gulliver et al. disclose that the variable light chains of the bispecific antibody disclosed in Mallender et al. are nearly identical, and therefore are deemed by the Examiner to have 98% identity, because Applicants have previously remarked that light chains having at least 98% sequence identity are "nearly identical." Applicants disagree. Neither Mallender et al. nor Gulliver et al. teach that the bispecific antibody of Mallender comprises light chains that are 98% identical to each other. Applicants respectfully submit that the Examiner is improperly using Applicants' definition of "nearly identical" as used in relation to the present application, to define the meaning of this phrase in the cited art. Applicants' remarks were not directed to the meaning of the phrase "nearly identical" in the Gulliver et al. reference, or in any other cited art.

Applicants submit that the Mallender et al. reference as evidenced by Gulliver et al. does not anticipate Applicants' claim 47 in the least, because Mallender et al. does not teach a first and second multimerization domain and does not teach a bispecific antibody where the first binding site and the second binding site has the same variable light chain. Applicants, therefore, respectfully request withdrawal of the rejection.

35 U.S.C. § 103

Claims 30-51 were rejected under 35 U.S.C. § 103(a) as unpatentable over Reddy et al., Vaughan et al., and Zhu et al. Applicants traverse this rejection.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) there must be suggestion or motivation to modify the reference or combine the reference teachings, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art; and 3) a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, in the least, because there is no motivation to combine the references in the manner suggested by the Examiner, the references even when combined do not teach all the limitations of the claims, and because there would be no reasonable expectation of success in doing so.

Applicants' claims 30-33 are directed to methods of forming bispecific antibodies wherein the same antibody variable light chain interacts with a first variable heavy chain domain to form a first binding domain and with a second heavy chain variable domain to form a second binding domain. Applicants' claims 33-38 and 41-44 are directed to methods and host cells for preparing a bispecific antibody wherein the first and second variable light chain domain have at least 98% sequence identity and only differ in amino acid positions outside of the CDRs. Claims 36-38 and 43-44 are directed to host cells and methods for preparing a bispecific antibody, wherein each of the multimerization domains comprises a residue with a free thiol positioned so that a disulfide bond is formed between the first and second polypeptides. Claims 45-51 are directed to a method for preparing a bispecific antibody whereby a light chain variable domain is selected that has at least 98% sequence identity to each variable light chain domain of each of two different antibodies.

Reddy et al. teaches a method of producing a BsMAb recognizing both CEA and doxorubicin for site-specific drug delivery. This reference does not discuss any problems with the formation of the bispecific antibodies and is not concerned with the pairing of light and heavy chains. Reddy et al. does not teach or suggest a method of forming bispecific antibodies by selecting a first and second variable light chain domain having at least 98% sequence identity in amino acid positions outside of CDRs or selecting light chains that have the same sequence. The reference also does not teach or suggest a method where the first variable light chain domain interacts with the first or second variable heavy chain and the second variable light chain interact with the first or second heavy chain.

The Vaughan et al. reference discloses and is directed to an scFv phage library of naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities. However, this reference does not teach or suggest that such light chains should be selected over other light chains or that these light chains can or should be used in bispecific antibodies. In addition, Vaughan et al. does not describe or suggest that a first and second variable light chain domain can have at least 98% sequence identity in amino acid positions outside of CDRs in a bispecific antibody, or forming a bispecific antibody comprising a first and second binding domain with the same light chain. Since this reference does not teach or suggest a method of obtaining bispecific antibodies, the reference does not teach or suggest selecting light chains having at least 98% sequence identity or even 100% sequence identity over other light chains to prepare a bispecific antibody in high yield.

Nor does the Zhu et al. reference remedy these deficiencies. This reference is directed to the use of domain interface engineering strategies to enhance the preference of a pair of single chain Fv proteins to form heterodimers rather than homodimers. Zhu et al. nowhere discuss, however, any problems with the pairing of light and heavy chains. Zhu et al. do not teach or suggest a method of forming bispecific receptors by selecting a first and second variable light chain domain having at least 98% sequence identity in amino acid positions outside of CDRs, or at least 98% sequence identity to a variable light chain domain of each of two antibodies that bind different antigens, or selecting light chains that have the same sequence.

Therefore, Applicants submit that none of the references, alone or in any combination, disclose all of the elements of Applicants' claims. In the least, the references in combination fail to disclose a method of forming a bispecific antibody that has the same light chain variable domain, variable light chain domains that have at least 98% sequence identity and differ at amino acid positions outside of CDRs and selecting a light chain variable domain that has at least 98% sequence identity to each variable light chain domain of a first and second antibody.

Applicants submit that one of skill in the art would not be motivated to combine or modify the references as cited by the Examiner. As discussed previously, the Reddy et al. reference is directed to showing the functionality and dual specificity of specific bispecific antibodies. There is no discussion in this reference of any problems with making bispecific

antibodies. This reference is not directed to methods for preparing bispecific antibodies and do not teach or suggest selection of first and second variable light chains that have at least 98% sequence identity or even 100% sequence identity as a solution to preparing and/or increasing yield of bispecific antibodies.

The Vaughan et al. reference is also not directed to methods of preparing bispecific antibodies. The Vaughan et al. reference is directed to forming a diverse scFv phage library of naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities. However, this reference does not describe bispecific antibodies or any concerns regarding the methods for producing bispecific antibodies. Thus, this reference does not teach or suggest that light chains that have at least 98% sequence identity or even 100% sequence identity should be selected over other light chains to improve yield of bispecific antibodies. Moreover, Vaughan et al. did not teach or suggest that ScFv with identical light chains for any two antigens could be found in high frequency of possible pairwise combinations of two different antigen specificities.

The Zhu et al reference is directed to the use of domain interface engineering strategies to enhance the preference of a pair of single chain Fv proteins to form heterodimers rather than homodimers. As discussed previously, Zhu et al. nowhere discuss, however, any problems with the pairing of light and heavy chains. Zhu et al. do not teach or suggest a method of forming bispecific receptors by selecting a first and second variable light chain domain having at least 98% sequence identity in amino acid positions outside of CDRs, or at least 98% sequence identity to a variable light chain domain of each of two antibodies that bind different antigens, or selecting light chains that have the same sequence.

Thus, Applicants submit that the cited references provide no motivation to combine or modify the references to obtain Applicants claimed invention. Applicants submit the Examiner is using hindsight reconstruction.

Applicants also submit that there would be no reasonable expectation of success that the claimed method would result in the efficient production of bispecific antibodies. The Vaughan et al. reference does not teach or suggest selecting light chain variable domains that have 98% sequence identity or even 100% sequence identity in a bispecific antibody. Although the Vaughan et al. reference discloses that the same light chain is sometimes paired with different

heavy chains, there is no disclosure in Vaughan that a light chain having at least 98% sequence identity can be found at high frequency of pairwise combinations of antibodies of different specificities. The Zhu et al. reference and the Reddy et al. reference also do not teach or suggest that light chain variable domains that have at least 98% or even a 100% sequence identity between antibodies that have different antigenic specificity occurs at great enough frequency to allow for the selection or identification of such variable light chain domain. Thus, Applicants submit even if the references are combined they do not provide a reasonable expectation of success.

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103 rejection of the claims, because the references when combined do not disclose all of the elements of Applicants' claimed invention, there is no motivation to combine the references cited by the Examiner, and there would be no reasonable expectation of success based on these references a method for preparing a bispecific antibody as claimed.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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